Amendments to the Specification

Please replace the paragraphs at page 11, line 15 through page 12, line 33 with the following amended paragraphs:

FIGURE 1 Depicts multiple sequence alignment of the evolutionarily conserved EGF domains for different known ErbB-ligands identified for worms (C. elegans), insects (Drosophila melanogaster) and mammals (humans or mice). Sequences ~~shaded in grey~~ marked in boldface and underlined demonstrate invariant residues in this alignment. Six cysteine residues are thought to be required for the formation of three disulfide loops within the domain for all these known ligands. An invariant Glycine and Arginine residue, considered critical for high-affinity ligand-receptor binding (boxed region). This multiple sequence alignment was generated by ClustalX (version 1.81) with modification, using the following protocol: The mammalian sequences were independently aligned by ClustalX (default parameters). This was repeated for the invertebrate ligands. These alignments were then treated as independent profiles, where the profile of mammalian sequences was aligned against the profile of invertebrate sequences, once again using clustalX (profile mode). All calculations were performed using default program parameters.

FIGURE 2 Represents multiple sequence alignment of Argos primary protein sequences published for three independent insect species, Drosophila melanogaster, Drosophila virilis and Musca domestica. Two cysteine-rich domains defined as A1 and A2 and the EGF domain are marked in bold-set and underlined. The definitions demarking these domains have been borrowed from elsewhere (Howes et. al, 1999). Regions of highly conserved residues indicate the presence of critical domains within the Argos protein sequences. Similarly, the Musca domestica protein sequence demonstrates that an

invariant Arg residue found in the EGF domain for all other receptor agonists (see Figure 1) is not necessarily conserved in insect Argos (boxed region). * denotes invariant residues; : denotes conserved residues; . denotes Semi-conserved residues.

FIGURE 3 Shows multiple sequence alignment of the receptor-modulating EGF domain encoded by different mammalian ErbB-ligands. Multiple sequence alignment of the receptor-binding EGF domain encoded by different mammalian ErbB-ligands were used as an input from which to generate a sequence profile in order to perform profile searches against various databases using a Compugen (hosted at EMBL) Bioccelerator. This alignment was generated by ClustalX version 1.81 and with minor manual modification. * = Invariant residues, : = Conserved residues, . = Semi-conserved residues.

FIGURE 4 presents an examination of the genomic locus encoding "Exon A" of the EGF domain for the Neuregulin/EGF ligand family. The genomic sequence encoding Exon A for each ligand was extracted from the NCBI human (or where indicated mouse) genomic database. The genomic sequence was then translated, this including extended sequence running into and beyond the 5' exon:intron splice junction which typically demarks the end of Exon A. This 'extended Exon A' potentially encodes an invariant in-frame stop codon positioned at precisely the same coordinate for all ErbB ligands relative to cysteine 4 of the EGF domain. The protein sequences of the full-length EGF domains are aligned in this figure against the translated sequence of extended Exon A. Exon A and Exon B boundaries are ~~alternatively shaded~~ designated above the alignment. The presence of a stop codon is denoted by an asterisk(*). Dotted lines (....) indicate that the exon-encoding sequences extend beyond this alignment. The protein

sequences present in this figure are listed herein as indicated (SEQ ID NOS:14-26, and 73-84). The nucleotide sequences encoding extended Exon A for each ligand are also provided (SEQ ID NOS:128-139). The EGF domain encoding full length mouse epigen is given here, as the human sequence was not available at the time of this analysis. The "extended exon A" sequence derived from genomic data are provided for both species. *Figure 4A* presents the NRG1, NRG2, NRG3, NRG4, EGF, TGF and betacellulin sequences, and *Fig. 4B*, the amphiregulin, HB-EGF, epiregulin and epigen sequences.

Please delete the paragraph beginning at page 13, line 14 and insert in its place the following new paragraph:

FIGURE 5B provides an examination of the genomic locus encoding different EGF domains for human TGF alpha and EGF, and *Figure 5C* does the same for Notch-1. The protein sequences for TGF alpha (i), EGF (ii) and Notch-1 (iii) were blasted against the human genomic database (tblastn; NCBI), to examine the exon structure for these genes. The EGF domains of these protein sequences were identified using the SMART database with manual adjustment, where flanking sequences have been ignored. These domain sequences were aligned (Clustalx version 1.81; standard parameters). An underline indicates the genomic topology, demarking exon-exon boundaries within a particular EGF domain. The coordinates of each EGF domain is given in each case. For example, the first EGF domain which spans amino acids 24-57 for Notch-1 is shown as EGF_24_57. The protein sequences and genomic sequences used to examine TGF alpha, EGF and Notch-1 were derived from the NCBI accessions [P01135, NT_022184.9], [NP_001954.1, NT_028147.9] and [AAG33848, NT_024000.13] respectively. Of the aligned domains, the exceptional examples of ErbB-receptor-activating

EGF domains are typed in bold-set and demarked with an asterisk (*). Of the forty four EGF domains examined which do not directly activate ErbB receptors (thirty six domains for Notch-1 and eight domains for EGF), only two of these (Notch-1 EGF domains number 1 and 30) harbor an exon-exon boundary which splits Cysteine 1-4 and Cys 5-6. The first EGF domain of Notch-1 is not fully underlined, due to the lack of this segment of genomic sequence found in the BLAST alignment.

Please replace the paragraph at page 14, lines 1-6 with the following amended paragraph:

FIGURE 6 shows the Biocore binding profiles for mEGF(1-32) *(Fig. 6A)* & hNRG2(1-32) *(Fig. 6B)* against immobilized betacellulin. mEGF(1-32) and hEGF(1-32) at the indicated concentrations were injected oer the surface of a Biacore chip with immobilized betacellulin and the resulting sensor curves were subtracted against a blank channel to yield the specific responses indicated. The results indicate low affinity interaction between each of the two peptides shown with Betacellulin. (RU - Resonance Unit)

Please replace Table 5, on page 64 beginning at line 7 with the following amended table:

Name	**Site**
Entrez Server	~~http://~~www.ncbi.nlm.nih.gov/Entrez/ www.ncbi.nlm.nih.gov/Entrez/
Blast Server	~~http://www.ncbi.nlm.nih.gov/blast/~~ www.ncbi.nlm.nih.gov/blast/
Compugen Bioccelerator Server (EMBL)	~~http://eta.embl-heidelberg.de:8000/misc/~~ eta.embl-heidelberg.de:8000/misc/
Compugen PROFILEWEIGHT	~~http://eta.embl-heidelberg.de:8000/profw/~~ eta.embl-heidelberg.de:8000/profw/

Emboss Transeq Server	~~http://www.ebi.ac.uk/emboss/transeq/~~ www.ebi.ac.uk/emboss/transeq/
SMART Server	~~http://smart.embl-heidelberg.de/~~ smart.embl-heidelberg.de/
ClustalX	~~ftp://ftp-idbmc.u-strasbg.fr/pub/ClustalX/~~ idbmc.u-strasbg.fr/pub/ClustalX/

Please replace the paragraph at page 68 beginning at line 31 with the following amended paragraph:

Aqueous solutions of the synthetic peptides mEGF (1-32) hNRG2 (1-32) (1mg/mL) were provided for analysis. 1.0 μL samples of each of these solutions were spotted onto a Perseptive Biosystems 10 x 10 MALDI target. A 10 mg/mL solution of α-cyano-4-hydroxycinnamic acid (Sigma-Aldrich Pty. Ltd, Sydney, Australia), which had been purified by recrystalisation from aq. Ethanol, was prepared in 60% aq. Acetonitrile, 0.1% TFA immediately before use and 0.5 μL of this solution was added to each sample spot on the target. Samples were allowed to air dry at room temperature. TOF-MS data was acquired using a QSTAR Pulsar *I* mass spectrometer (Applied Biosystems, U.S.A.) equipped with an oMALDI II source. Ionisation was performed using a 337 nm wavelength nitrogen laser with a pulse rate of 20 Hz and a power level of 14.8 μJ. Data from [Glu^1]-fibrinopeptide B (Auspep Pty. Ltd, Melbourne, Australia) was used for TOF calibration. Mass accuracy in TOF-MS mode was better than 35 ppm. The theoretical monoisotopic molecular weights of the peptides were calculated using Protein Prospector (1) at the Asia-Pacific website (~~http://jpsl.ludwig.edu.au/~~ jpsl.ludwig.edu.au/). The molecular mass of refolded peptide hEGF (1-32) was determined independently on a different

device, but by using a similar MALDI mass spectrometry approach. The results are summarized in Table 7.